Walter Reed Army Institute of Research
Human Subjects Protection Branch
Standard Operating Procedure

SOP Title	**NON-COMPLIANCE PROCEDURES**	SOP No.	**UWZ-C-606**
		Version	**.02**
Effective Date	MAR 14 2012	Page	1 of 14

Signatures and Dates:

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Review/Approval for unchanged documents

Date	Author	QA Review	Approving Authority

1. **Purpose/Applicability:** This Standard Operating Procedure (SOP) sets forth the requirements concerning allegations of non-compliance reported to the Walter Reed Army Institute of Research (WRAIR) Institutional Review Board (IRB) for human subjects research conducted at WRAIR, WRAIR subordinate laboratories or by WRAIR personnel.

   Under the regulations (21 CFR 56, 32 CFR 219, also known as the common rule or 45 CFR 46 [for studies receiving Department of Health and Human Services – DHHS – funding]), the IRB has the authority to suspend or terminate approved research that is not being conducted in accordance with established requirements and regulations, or that has been associated with unexpected harm to subjects. The IRB must consider minimizing risk to subjects enrolled in research; protecting the informant from retaliation; protecting the reputations of the investigators and research staff until a determination is made, when appropriate; ensuring a fair process of investigation; appointing appropriate individuals to conduct the investigation; developing procedures for fact finding; documenting the investigation and the fact finding process; determining corrective actions or sanctions; referring matters of research misconduct to appropriate institutional officials (IOs); and reporting to department or agency heads and funding agencies.

   Food and Drug Administration (FDA) regulated research: Under 21 CFR 56.108(b), IRBs shall promptly report to appropriate IOs and the FDA, when appropriate [; any instance of serious or continuing non-compliance with the regulations or the requirements or determinations of the IRB [56.108(b)(2)]; or any suspension or termination of IRB approval [56.108(b)(3)].

   DHHS or Department of Defense (DoD) regulated research: Under 32 CFR 219 and 45 CFR 46, the IRB shall promptly report any suspension or termination of approval [32 CFR 219.113 and 45 CFR 46.113] and any serious or continuing non-compliance with the regulations or the requirements or determinations of the IRB, to the investigator, appropriate IOs, and the department or agency head.

   This SOP establishes the process for receiving, investigating, managing and reporting allegations of non-compliance with regulations governing the use of human subjects in research, IRB determinations, and/or the research protocol.

   This SOP applies to WRAIR Investigators, IO, WRAIR IRB, WRAIR IRB Administrative Director, and the Human Subjects Protection Branch (HSPB) Staff.

2. **Responsibilities:**

a. The WRAIR IRB considers all allegations of non-compliance according to this SOP, and notifies all parties involved of its determinations regarding the reports.

b. The HSPB supports the WRAIR IRB in fulfilling their responsibilities.

c. The IO, in consultation with the IRB Chairperson and IRB Administrative Director will determine how the allegation will be investigated. The IO reviews the recommendations of the WRAIR IRB and determines which corrective actions are appropriate and may include additional actions as deemed appropriate.

3. **Investigator Guidance and Requirements:**

The Principal Investigator (PI) is expected to:

a. Respond to all requests for information from the WRAIR IO, IRB or IRB Administrative Director.

b. Comply with any determinations made by the WRAIR IRB and the IO regarding the research.

4. **Materials and Equipment:** Not Applicable.

5. **Procedures:**

a. Receipt and Investigating:

1. Upon receipt of an allegation of non-compliance involving human subjects research, the HSPB personnel receiving the report promptly notifies the WRAIR IRB Administrative Director (or designee). HSPB logs the initiation of the report in the database for the study. (Appendix A is utilized to record, in as much detail as possible, the information received.)

2. Possible sources from which allegations of non-compliance may come are:

a) Research participants or their friends or family[for example: participant's legally authorized representative];

b) DoD Research Monitor;

c) Reports of protocol non-compliance (including, but not limited to: deviation reports, continuing review reports, information from sponsor's monitoring letters or other correspondence);

d) Findings discovered during routine compliance monitoring (Refer to WRAIR SOP UWZ-C-633);

e) Failure or repeated failures of the investigator to file requested reports to the WRAIR IRB;

f) Institutional personnel;

g) Publications involving WRAIR investigators engaged in human subjects research without WRAIR IRB approval of the referenced study or studies;

h) Office of Human Research Protections (OHRP) or FDA warning letters/debarment regarding an investigator or a study;

i) Media or anonymous sources.

3. The initial report is promptly provided to the IO, IRB Chair (or designee), IRB Administrative Director, and the Compliance Officer. Based on the nature and substance of the allegation or expertise required during the investigation, the IO may delegate the investigation to an experienced IRB member, and experienced IRB staff person, a subcommittee, or other qualified individuals. Consultants may also be involved.

The WRAIR IRB Chair or designee determines if immediate suspension of subject enrollment is required to protect the rights, safety and welfare of subjects until the allegation is investigated. If immediate suspension is necessary, this will be reported to the IO and fully convened IRB at the next scheduled meeting

4. Additional information regarding the report is obtained by the investigation designee including, but not limited to the following:

a) Interviews or inquiries with the authors of the report or complaint;

b) Written requests for follow-up with the authors of the report or complaint, Sponsor, Monitor or other regulatory person;

c) Discussions with the PI or other study personnel;

d) Discussions with subjects and/or their legally authorized representatives;

e) Requests of records from the PI or study personnel;

f) Request of IRB Directed (For Cause) monitoring (Refer to WRAIR SOP UWZ-C-634)

5. The IRB Chair, fully convened IRB, WRAIR IRB Administrative Director, or a subcommittee may determine that a directed (for cause) review is merited. If so, the review will be conducted as soon as possible, but within a time frame, commensurate with the seriousness of the allegations and geographical location of the study site and/or investigator (Refer to WRAIR SOP UWZ-C-634- Directed Monitoring).

6. The IRB or the IRB Administrative Director may elicit assistance from local points of contact (POCs) also known as the site-specific Human Protections Coordinators (HPC) for the purposes of the directed-review and investigation (Refer to the WRAIR Human Research Protection Program [HRPP]).

7. The investigation of non-compliance allegations will be documented. Any requests for additional or supporting information are sent by email, fax, or mail.

8. Protocol Investigators and others who may have relevant information should have the opportunity to provide input during the investigation. Every effort must be made to protect the identity of Institutional Personnel (also known as "Whistle-blowers") before, during, and after an investigation.

9. Those against which allegations of non-compliance have been made will be provided a description of the allegations, reasonable access to evidence and opportunity to respond and provide input.

10. If the investigation supports the allegation of non-compliance or if other instances of non-compliance are identified, the investigation results will be

reported to the convened IRB. The report will contain, at a minimum, a detailed description of the allegations, investigation findings, and recommendations for IRB findings that may include determinations or non-compliance, serious non-compliance, and /or continuing non-compliance. Only the convened IRB can make a determination of serious and/or continuing non-compliance.

11. If the investigation fails to support the allegation and no evidence or other instances of non-compliance is identified, the investigation results will be reported to the IO, IRB Administrative Director, and the Compliance Officer. The IRB Administrative Director in consultation with the IO may require additional investigation and/or referral of the investigation to the convened IRB.

12. The convened IRB will review the results of the investigation and recommendations. The IRB will:

a) Determine if the investigation was sufficient. If the IRB determines that the investigation was not sufficient, it may require additional investigation before making a determination regarding non-compliance. Alternatively, the IRB may refer the investigation to the next higher authority (HQ USAMRMC ORP HRPO) for further investigation if there is an institutional conflict of interest and/or the protocol in question was previously administratively reviewed by HRPO.

b) Accept or reject the recommendations that the IRB find that non-compliance occurred. If the IRB finds that there is non-compliance, the IRB must determine if the non-compliance is serious and/or continuing.

c) Review actions to correct the non-compliance (see section B (1). The IRB must take into account the situation and identify actions that are appropriate given the seriousness and extent of the non-compliance. The IRB must identify a well-defined timeline for the corrective action plan. When appropriate, the PI will develop and provide for review by the IRB a corrective action plan for the non-compliance.

d) IRB meeting minutes must reflect the determination of the IRB with regard to non-compliance and include the corrective action plan as a recommendation to the IO.

e) Study investigators must be promptly provided written notification of the IRB's determination along with a statement of the reasons for its decision and corrective action plan as stipulations actions. Study investigators must have an opportunity to respond to the IRB in person or in writing.

b. Managing Non-Compliance

(1) Appropriate corrective action must be taken to protect human subjects and to manage the non-compliance. The IRB must identify appropriate actions. Such actions may include, but are not limited to:

a) Suspension or termination of the research;

b) Temporary suspending new subject enrollment in a protocol;

c) Notification to subjects of non-compliance;

d) Requiring the investigator to destroy all data from research involving subjects obtained without IRB review and approval;

e) Requiring the investigator to make all data anonymous by removing all codes, identifiers, and identifiable information;

f) Requiring the PI and/or study staff training in Good Clinical Practices, or alternative human subjects protection training;

g) Requiring investigator supervision by a qualified mentor and /or hiring of new, qualified staff;

h) Imposing sanctions on the PI;

i) Suspending individual investigators from participation in the research protocol;

j) Requiring modification to the protocol or consent form;

k) Re-consenting subjects;

l) Requiring additional safeguards such as more frequent IRB continuing review, third party monitoring, or auditing of research/consent process/recruiting and/ or site visits;

m) Notifying funders, partners, or collaborators of the findings of non-compliance and/or required corrective actions, if applicable;

n) Additional decisions may be needed regarding the status of data/specimens collected and the appropriateness of publicizing the study results;

o) Other actions as appropriate.

(2) Should the IRB determine that the incident is isolated and resolved, a letter will be sent from the IO to the PI (and copied to the sponsor and other involved agents) describing resolution based on the documentation and results of the investigation. Suspension of enrollment is lifted. Should the IRB determine a new continuing review interval, this date is stated in the letter.

(3) Should the IRB make a determination of non-compliance the PI will be sent a separate letter detailing the IRB's determination, length of suspension or termination of IRB approval, corrective action plan, any additional requirements, sanctions or restrictions and a request for a response in writing.

(4) The IRB, HSPB staff or IRB Administrative Director must document that all corrective actions have been completed in a satisfactory manner and timeframe. The IO will be provided this documentation and may impose additional corrective actions or sanctions for investigators who fail to satisfactorily complete required corrective actions in the allotted timeframe.

(4) Regarding Suspensions:

The WRAIR IRB Chair or designee determines if immediate suspension of subject enrollment is required to protect the rights, safety and welfare of subjects until the allegation is investigated.

The length of any suspension is recommended by the WRAIR IRB Chair, or fully convened IRB, to the IO and based on the seriousness of the preliminary information received or determined non-compliance.

If a suspension is merited, a meeting between the IRB Administrative Director or WRAIR IRB Chair and PI is called within 30 days. The PI should develop a corrective action plan for recommendation to the full IRB.

Should such a determination be made to suspend the protocol either singly, or in conjunction with other protocols under the same PI or site, the WRAIR IRB Chair, IOs or designees notify the following (if applicable): PI, Co-PIs, Department Chief, Division Director, IO, Office of the Science Director, Compliance Officer, U.S. Army Medical Research and Materiel Command Office of Research Protections Human Research Protections Office (USAMRMC ORP HRPO), Army Human Research Protections Office (AHRPO) and sponsors. This notification is made by telephone, fax, or email, and may be followed by mail.

c. Reporting Non-Compliance:

(1) Once the IRB of record makes a finding of serious non-compliance or continuing non-compliance, the findings must be promptly reported to the HQ USAMRMC ORP HRPO regardless of the risk level of the study of the type of HQ level review the study received. Notifications are done by phone to the Director, ORP HRPO, followed by a written letter. (See Appendix B for required reporting information)

(2) Findings of serious or continuing non-compliance must also be promptly reported to the AHRPO in accordance with ALARACT 031/2008, paragraph 4c (1). Notifications are done by phone to the Director, AHRPO, followed by a written letter. All findings of serious non-compliance will be reported through AHRPO to the Director, Defense Research and Engineering in accordance with DoD Instruction 3216.02.

(3) As appropriate, other federal agencies such as the OHRP or FDA may require prompt reporting of findings of serious and/or continuing non-compliance. Reporting to these agencies will depend on the funding for the study under which non-compliance was determined and/or whether the study is subject to FDA regulations. It is the responsibility of the IO to ensure reporting to these agencies in accordance with OHRP and FDA regulations.

(4) For FDA regulated studies sponsored by the Office of The Surgeon General of the Army, the FDA will be notified by the U.S. Army Medical Materiel Development Activity (USAMMDA) of any determination to further suspend or terminate approval (Refer to AR 40-7).

(d). Any response from the PI, FDA, OHRP, USAMRMC ORP HRPO, sponsor or other involved persons will be reviewed by the IRB Chair, fully convened IRB, and IO.

(e) Copies of all correspondence and reports are maintained in a separate file in the DHSP.

6. **Explanation of Abbreviations and Terms:**

AHRPO	Army Human Research Protections Office
ALARACT	All Army Activities
Continuing Non-compliance:	A pattern of non-compliance that suggests a likelihood that, without intervention, instances of non-compliance will recur, or that indicates an unwillingness to comply with or a lack of knowledge of Federal and DOD regulations, policy, and law, determinations or requirement of the IRB and/or Headquarters, USAMRMC (HQ USAMRMC) or the research protocol
Department or Agency Head	Director, Defense Research and Engineering (DDR&E)
DOD	Department of Defense
FDA	Food and Drug Administration
HQ	Headquarters
HPC	Human Protections Coordinators

HRPP	Human Research Protections Program
Human Subject:	A living individual about whom an investigator (whether professional or student) conducting research obtains 1) data through intervention or interaction with the individual, or 2) identifiable private information.
Institutional Official	WRAIR Commander
Institutional Review Board (IRB):	WRAIR Institutional Review Board, the ethical review committee for research involving human subjects at WRAIR, its CONUS detachments or Overseas Laboratories, or when WRAIR funding, facilities or personnel are involved in any way (investigator, medical monitor, consultant, collaborator, etc.). This includes protocols for which recruitment of subjects is through WRAIR.
IRB "For Cause" Termination:	An official action by the IRB to stop the conduct of a study. Termination does not include: (1) voluntary termination of a study by an investigator (unless the investigator requests termination of the study due to unanticipated problems); (2) studies whose IRB approval has expired (unless the IRB determines that the researcher continues to conduct the study despite notification that IRB approval has expired).
Non-compliance:	Failure of a person, group or organization to act in accordance with a law, regulation, or policy governing human subjects research, the requirements and/or determinations of the overseeing IRB, or the research protocol..
Human Subjects Protection Branch (HSPB):	Human Subjects Protection Branch, WRAIR, is the administrative branch of the WRAIR IRB.
OHRP	Office of Human Research Protection, U.S. Health and Human Services
PI	Principal Investigator or WRAIR POC
POC	Point of Contact

Prompt Notification	Providing initial notification of an event promptly (within 48 hours) after it has been identified. All required reporting must occur without delay.
Research:	Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.
Directed Monitoring	An established program that serves to assess whether human research protocols are being conducted in compliance with human subjects regulations, WRAIR policies, and the IRB approved protocol.
Serious Non-compliance:	Non-compliance that could adversely affect the rights, safety or welfare of participants; place participants at increased risk of harm; cause harm to participants; affect subjects' willingness to participate in research; or damage or compromise the scientific integrity of research data.
SOP	Standard Operating Procedure
Substantive Modification:	A change that has the potential of materially affecting the risk/benefit assessment of the study.
Suspension of IRB Approval:	An official action by the IRB to suspend the conduct of a study. Suspension does not include protocol-planned suspension (e.g., for interim data analysis).
USAMRMC:	United States Army Medical Research and Materiel Command serves as the Command Headquarters for the WRAIR.
USAMRMC ORP HRPO:	United States Army Medical Research and Materiel Command, Office of Research Protections, Human Research Protections Office.
Whistleblower:	An individual who reports information regarding potential non-compliance issues, generally this is institutional staff.
WRAIR	Walter Reed Army Institute of Research

References:

Reference Number or Authors	Document Title
DODI 3216.02	*Department of Defense Instruction- Protections of Human Subjects and Adherence to Ethical Standards for DOD Supported Research,* 20 October 2011.
AR-40-68	*Clinical Quality Management,* 26 February 2004.
AR-70-25	*Use of Volunteers as Subjects of Research,* 25 January 1990
AR-40-7	*Use of Food and Drug Administration – Regulation Investigational Products in Humans Including Schedule I Controlled Substances*
ALARACT 031/2008	Army Human Research Subject Protection Requirements
Command Policy 2004-11	Standard Operating Procedures (SOP) for Food and Drug Administration (FDA) Regulated Activities within the Command, 1 September 2004.
Command Policy 2010-03	Investigating, Managing, and Reporting Non-Compliance with Human Subjects Research Regulatory Requirements for US Army Medical Research and Materiel Command (USAMRMC) Intramural Research
WRAIR IRB Charter	Walter Reed Army Institute of Research Institutional Review Board (WRAIR IRB) Charter.
WRAIR HRPP	WRAIR Human Research Protection Program (HRPP)
ICH-GCP-E6	*Guideline for Good Clinical Practice.*
OHRP Guidelines	*Guidelines for Formulating Written HURC Policies and Procedures, 11 July 2002.* http://ohrp.osophs.dhhs.gov/HURC/HURC_guidebook.htm
Titles 21, 32 and 45	*Code of Federal Regulations*

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WRAIR SOP UWZ-C-633	Routine Monitoring for Human Subjects Research Compliance
WRAIR SOP UWZ-C-634	Directed Monitoring of Human Subjects Research

7. **Forms and Appendices:**

Form or Appendix Number	Title
Appendix UWZ-C-606-A	Allegation of Non-Compliance Intake Form
Appendix UWZ-C-606-B	Elements of a Non-Compliance Report
Appendix UWZ-C-606-C	Non-Compliance Process Checklist

8. **Document Revision History:**

Version Number	Brief Description of Changes	Effective Date
.00	New	15 Dec 2006
.01	Biennial review, revised to update organization names, incorporate relevant regulations, and include updated policies and procedures.	14 Jan 2009
.02	Biennial review, revised to incorporate relevant regulations, and include updated policies and procedures.	17 Feb 2012

Date:

HSPB staff member taking report:

Name of person reporting:

Site of Non-Compliance Allegation:

Contact information of person reporting:
Phone
Cell
Fax
Email
Address

Relationship to issue/protocol:

Type of Report (phone call, email, fax, etc):

Title and WRAIR Protocol # (if applicable):

PI name:

PI's Department & Division/Branch:

Brief Summary of the nature of the report:

Actions taken/planned to address the non-compliance:

Recommendation to IRB:

Printed Name/Signature HSPB Staff **Date**

Printed Name/Signature Reviewer (or designee) **Date**

Relay to person reporting that you will gather information and the Deputy Director, HSPB, Director, HSPB, or Chair, WRAIR IRB will contact them as soon as possible. Be sure to thank the person reporting and reassure that the information will be reviewed.

Appendix B	**Required Elements of Serious and/or Continuing Non-Compliance Report**	SOP No.	**UWZ-C-606**
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1. Name of the Institution conducting the research:

2. Site of the non-compliance:

3. Title of the Research Protocol:

4. Name of the Principal Investigator (PI) or Site Specific PI:

5. WRAIR # and other Log Number(s) of the research project assigned by the IRB

6. Proposal or award number of any applicable federal award(s) (e.g. grant, contract, or cooperative agreement):

7. A detailed description of the non-compliance, along with a recommendation for finding(s) that may include determinations of non-compliance, serious non-compliance, or continuing non-compliance:

8. Actions taken or planned to address the non-compliance (e.g. educate the investigator, suspend the protocol, suspend the investigator, etc)

Appendix C	**Allegation of Non-Compliance Process Checklist**	SOP No.	**UWZ-C-606**
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Date:

Protocol Title:

1. Allegation of Non-Compliance:

[ ] Complete Intake Form

2 .Promptly notify:

[ ] IRB Administrative Director and IRB Chair

[ ] Log receipt of report into HSPB Database

3.Provide Initial Report to:
[ ] IRB Administrative Director (Director, HSPB)
[ ] IRB Chair
[ ] Institutional Official
[ ] Compliance Officer

[ ] If immediate suspension of enrollment necessary, add the N/C intake report to Agenda of next IRB Meeting

4. [ ] IO/ IRB Chair/ IRB Ad Dir Decision on Investigation Process

5. [ ] Execution of Investigation Process

6. [ ] Management of Investigation Process

7. Allegations Substantiated

[ ] Identify Specific regulations/ policy or procedures that were not followed

[ ] Report to full committee for decision of non-compliance, serious non-compliance and/or continuing non compliance The report will contain, at a minimum, a detailed description of the allegations, investigation findings, and recommendations for IRB findings that may include determinations of non-compliance, serious non-compliance, and /or continuing non-compliance

[ ] Corrective Action Plan Developed

[ ] IRB Recommendation to IO for final determination

Reporting Requirements:

[ ] Report Serious or Continuing Non-Compliance to :
[ ] MRMC ORP HRPO
[ ] AHRPO
[ ] DDR&E by AHRPO

[ ] As applicable to the funding and type of research:
[ ] HHS
[ ] FDA (if USAMMDA OTSG Sponsor they will notify FDA)
[ ] Collaborating Institutions
[ ] Funding Agency

7.Allegation NOT Substantiated

[ ] written communication to PI of unsubstantiated findings of allegation of non-compliance

8. Follow Up Procedures:

[ ] Document that all corrective actions have been completed in a satisfactory manner and timeframe. Provide the IO this documentation. The IO may impose additional requirements/sanctions.

[ ] Retain documents in separate file specific to non-compliance.

[ ] Add any Determinations and outcomes of Non-Compliance to the Annual report Log to go to AHRPO.